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ARTIFICIAL OLFACTORY SENSING SYSTEM

The present invention relates to sensors for detecting analytes in fluids, such as liquids, gases and vapour mixtures, and particularly, but not exclusively, to sensors for use in non-spectroscopic gas/vapour sensing systems.

Artificial sensors that are as capable of detecting odours as the mammalian olfactory system have been sought after for some time. (Lundstrom et al (1991) 352; 47-50; Shurmer and Gardner (1992) Sens. Act B 8; H1). Traditionally, it was thought that the mammalian olfactory system was based on a "lock and key" molecular recognition approach, but recent developments have revealed a different mechanism where the olfactory system is thought to utilise probilistic repertoires of many different sensors to recognise a single odour (Reed (1992) Newan 8: 205-209; Lancet and Ben Aire (1993) Cir, Biol 3:669-671), thus removing the burden of recognition from highly specific receptors to a distributed pattern processing of the olfactory bulb and the brain (Kauer (1991) TINS 14: 79-85; De Vries and Baylor (1993) Cell 10(S): 139-149).

In the development of non-spectroscopic gas/vapour sensing systems, there are two distinct techniques: the quartz crystal microbalance (QCM) (Sauerbrey (1959) Z. Phys. 155:206; King (1964) Anal, Chem. 36:1735; Ballantine Jr et al (1997) Acoustic wave sensors, Academic Press, San Diego ISBN: 0-12-0775600-7) which detects changes in mass; and conductivity measurements based on chemoresistors (Pelosi et al (1998) Sensors and Sensory Systems for Advanced Robots, ed. P. Dario NATO ASI series, Springer, Berlin, F42:361; Bartlett et al (1989) Sensors and Activators 118:371; Pearce et al (1993) Analyst, 118:371). In both instances, a transducing element is coated with a sensing membrane, which may be an organic polymer, or an organic oxide, or

simply a functionalised self-assembled monolayer. The principle behind these analytical systems is that interactions between the membrane and the vapour can be measured by either an increase in mass (QCM), or change in electrical resistance (chemoresistor).

In QCM studies, the materials used are commonly non-conducting overlayers, while the materials used in the chemoresistor systems are commonly conducting polymers or oxides. Both systems are attractive in that by suitable choice of sensing materials, the transduced signals are capable of being sensitive to low levels of an analyte vapour and responsive to a wide variety of different analytes.

Both the QCM (Grate et al (1991) Sensors and Actuators B 3:85; Hierleman et al (1995) Sensors and Materials 7(3):179; Deng et al (1996) Analyst 121:671) and chemoresistor techniques have been expanded to utilise arrays of sensing elements. In these arrays, each element, or group of elements, has its own characteristic response to different vapours and thus suitable signal processing provides a means to identify the composition of an unknown vapour stream. The increasing sophistication of the data processing, including the ability to assess training or library data sets, has lead to the development of a number of commercial devices based on chemoresistors (for example Gardener (1997) Proc. 3rd East Asian Conference on Chemical Sensors, Seoul, Korea, Nov. 5th-6th, K4, 24).

More recently, an innovation has resulted in the manufacture of a chemoresistive sensor fabricated using a dispersion of carbon-black (Lonergan et al (1996) Chem. Matter 8:2298), or any other freely divided conducting material (Severin et al (1997) Abstracts of Papers of ACS, 213 (3): 35-BTEC), in a non-conducting polymer so forming a conducting membrane. Sorbtion of a vapour into such a matrix causes a change in the electrical resistance by influencing the percolation paths between

conducting particles within the polymer film. A consequence of this has been to greatly expand the variety of polymers and deposition methods which can be used in the chemoresistor sensor systems. Additionally, by using such polymer composites, interpretation of the measured resistance changes becomes simplified because it has been found that, below the percolation threshold of the composite, changes in conductivity are approximately linear with the single component vapour phase concentration. It has been proposed that the resistance change is proportional to the change in the volume of the polymer-composite.

Whilst previous attempts to combine QCM and chemoresistance measurements in vapour analysis have yielded some benefits (Slater (1991) Analyst 116:1125; Slater et al (1992) Analyst 117:1265; Yoshitio et al (1994) J. Chem Commun. 873; Nogorikawa et al (1995) 396:563), the numerous factors influencing conductivity mechanisms in the sensors have the consequence that responses are still difficult to relate to simple physical properties of the sensor and analyte.

It is an object of the present invention to provide a sensor for detecting analytes in a fluid which obviates or mitigates at least one of the aforementioned disadvantages of existing detector systems.

This is achieved by using at least two sensors, one sensor providing a response dependent on the volume-change of a first sensory region, and a second sensor providing a response dependent on the mass change of a second sensory region. The responses are combined to provide a response characteristic of the molecular density of the analyte.

By determining the molecular density of the analyte, it has been found that devising a fluid recognition system based on this approach is simpler and more reliable than prior art systems. A fluid may be a liquid or a gas or a mixture of these such as a fluid vapour.

According to a first aspect of the present invention there is provided a sensor array for detecting an analyte in a fluid, said sensor array comprising at least two different types of sensor elements, one sensor element having a sensor region responsive to said analyte by a change in volume and the other element having a sensor region responsive to said analyte by a change in mass, whereby the responses of said at least two sensor elements are combined to provide an output characteristic of the molecular density of the analyte.

Preferably, the volume-changing sensor is comprised of a composite material containing a polymeric matrix with electrically conducting regions of a second material, whereby the electrical properties of the composite material change with a change in volume as a result of absorption of the analyte to be detected.

The polymeric matrix of the composite material may be organic or inorganic.

Preferably also, the change in electrical properties of the composite material is a change in the resistance or charge capacitance of said composite material.

Preferably also, the volume-changing sensor includes electrically conductive and non-conductive regions.

Preferably, the volume-changing sensor is a carbon black doped chemoresistor. Alternatively, the polymer of the volume-changing sensor may be loaded with either silver/gold/other metallic colloid or cluster, a conducting polymer or a redox metal or organometallic complex.

Preferably, the electrodes of the volume-changing sensor are interdigitated.

The volume-changing sensor may be a capacitance/ complex impedance sensor. Alternatively, the volume-changing sensor may utilise an optical, thickness-sensitive technique such as surface plasmon resonance spectroscopy or ellipsometry or based on an optical

transmission through a coated fibre optic..

Preferably, the mass-changing sensor comprises an acoustic resonance device which is usually coated with the same polymer or coating as the volume-change device. The resonance device may or may not be loaded with a semiconductor component.

More preferably, the acoustic resonance device is a quartz crystal microbalance. Alternatively the acoustic resonance is generated by a surface acoustic wave device.

Preferably, the volume-changing sensor and mass-changing sensor are integrated on the same device or sensor structure. The volume-changing sensitive coating and mass sensors may, in addition, be coated with a perm-selective or in any other way selective coating.

According to a second aspect of the present invention, there is provided a system for detecting an analyte in a fluid, said system comprising an array of analyte sensors, each sensor on said array having at least two different sensor elements, whereby upon adsorption of said analyte, a sensing region of a first sensor-element responds to said analyte by a change in volume, and a sensing region of a second sensor element responds to said analyte by a change in mass, the combined response of the two sensor elements being characteristic of the molecular density of the analyte being detected and an electrical measuring device electrically connected to said sensor array for detecting the outputs of the sensors of said sensor array and processing means for processing the output of said sensors to provide an output signal indicators of the analyte in the fluid to be detected.

According to a third aspect of the present invention, there is provided a method of detecting an analyte in a fluid, said method comprising the steps of passing the analyte to a first sensing element providing a first output signal for said first sensing element in response to a volume-change caused by adsorption of said

analyte by said first sensing element,

passing the analyte to a second sensing element and providing a second output signal for said second sensing element in response to a mass change cause by adsorption if said analyte by said second sensing element, and

combining the first and second output signal to provide a signal characteristic of the molecular density of the analytes being detected.

Preferably the method includes the step of processing a plurality of first and second output signals from said sensors.

The signals can be processed serially or in parallel. Parallel processing is required when an array of sensors is used.

The method is used to distinguish between the presence of a mixture of analytes, or a single analyte, within a host fluid.

These and other aspects of the invention will become apparent from the following description when taken in combination with the accompanying drawings in which:-

Fig. 1 is a schematic diagram of a system for detecting analytes in accordance with an embodiment of the invention;

Figs. 2a, 2b are diagrammatic plan and side views of a volume sensor for use with the system of Fig. 1 for detecting and identifying analytes in fluids;

Figs. 3a, 3b are diagrammatic plan and side views of a mass sensor for use with the system of Fig. 1 for detecting and identifying analytes in fluids;

Fig. 4 is a graph showing variation of resistance and frequency with time for the sensors shown in Figs 2a, 2b for exposure to n-hexane (13mm Hg) water (9mm Hg) and chloroform (6mm Hg) in nitrogen; as a function of time;

Fig. 5 is a graph of the ratio of QCM frequency change to resistance change against liquid density of the vapour for a variety of different gases over a wide range of densities, and

Fig. 6 is a graph of percentage resistance change against percentage frequency resistance change for a range of different dicholormethane vapour concentrations in nitrogen detected by the sensor system shown in Fig. 1.

Reference is first made to Fig. 1 which illustrates an example of a system for identification of analytes in a fluid, in this case for detecting a volatile analyte in a liquid, the system incorporating a sensor arrays 10 having a plurality of analyte sensors 12, 14 for providing volume-change response and a mass change response respectively to allow the calculation of molecular density of the analyte as will be described. The system comprises a receptacle 16 having an unknown analyte or analytes in a host liquid 18. Nitrogen gas 20, is passed through the liquid 18 to create and carry the vapour produced through a tubing 22, via flow meters 24 to an electronic rotary valve 26 under the control of a computer 30. The vapour then eventually passes through a sensor chamber 32 which contains a plurality of the chemoresistor type sensors 12 for providing a volume response signal and the quartz microbalance crystal-type sensors 14 for providing a mass response signal. Detection of the analytes in the vapour from the host fluid 18 is performed in the chamber 32 by the sensor arrays 10 and identification of the analytes executed by the computer 16 linked to the sensor array via sensor electronics as will be described later in detail. Exhaust outlets 34, 36 are provided on the rotary valve 26 and sensor chamber 32 for subsequent use after detection of the analyte has been performed.

The sensor array comprises a plurality of chemoresistor-type sensors 12 and quartz microbalance crystal-type sensors 14 as best illustrated in Figs. 2a,2b and 3a,3b. The array of chemoresistors includes a plurality of compositionally different chemical sensors 12. A chemoresistor is an electronic resistance element

whose resistance changes on exposure to different chemical species and this change need not be a consequence of chemical bond formation, or chemical reactions, but can occur through simple juxtaposition of the chemical species and electronic resistance element. As best seen in Figs. 2a,2b, each sensor 12 comprises electrically conductive leads 42 electrically coupled to and separated by a chemically sensitive resistor 24. The leads 42 are interdigitated to maximise the signal-to-noise ratio and are made of copper.

The chemoresistors are fabricated by doping a non-conductive polymer 44 with conductive material such as carbon black such that the electrically conductive path 46 of conductive material between the conductive leads is interrupted by gaps of non-conductive polymer 44. The chemoresistors are fabricated as multifingered interdigitated electrodes 42 with gap sizes between electrodes ranging from about 1 to 100μm.

The non-conductive gaps within each electrode range in size from about 10 to 100μm, usually of the order of 100 angstroms to provide individual resistance of around 10 to 1000mΩ usually on the order of 100mΩ across each gap. As the volume of analyte is absorbed by the non-conductive layer, the path length and resistance of a given gap changes in direct response, resulting in a direct relationship of analyte permeation ($\Delta R \propto \Delta V$) of the conductive regions with resistance provided by the gaps between given electrodes.

A wide variety of conductive and non-conductive materials can be used, examples of which are found in the PCT application No. WO96/30750. Manufacturing techniques are also disclosed in this application and in any event well known in the art.

Reference is now made to Figs. 3a,3b of the drawings which depicts the quartz microbalance crystal (QCM) mass sensor 14. These are cut quartz crystals obtained from ICM Co, Oklahoma, USA and designed to operate at 10 MHZ.

Sensors are fabricated using a solution of. non-conducting polymer identical to that of the chemoresistor sensor 12 with which the sensor output is to be compared to define the molecular density of the analyte. The piezoelectric sensor 14 as illustrated in Figs. 3a,3b has a quartz crystal 48 with an active area defined by overlapping electrodes 49 in contact with the non-conducting polymer coating 50. The QMC sensor 14 oscillates at a frequency which is dependent on the mass of the crystal between the overlapping electrodes 49. Thus, the frequency of oscillation of the QMC is directly proportional to the mass of the polymer on the microbalance ($\Delta f \propto \Delta$ mass. Upon adsorption of an unknown analyte by the sensor 14, the resonance frequency of the microbalance changes as a result of the increase in mass of the crystal.

By combining the measurement of resistance which is proportional to the volume, and the measurement of frequency which is proportional to mass, the average molecular density of the polymer can be calculated as illustrated in the following relationship.

Change in resistance $\propto$ volume of change of polymer as a result of swelling on uptake of analyte

$$\Delta R \quad \propto \quad \Delta V \qquad \text{-----(1)}$$

Change in resonant frequency $\propto$ mass uptake of analyte by polymer

$$\Delta f \quad \propto \quad \Delta m \qquad \text{-----(2)}$$

Therefore the ratio of Δf to ΔR is proportional to the ratio of Δm to ΔV, which is directly proportional to molecular density.

At high vapour pressures, the resistance/frequency becomes non-linear and has been found to be dependent on the vapour concentration range and the loading of the conducting material. This can be accounted for using an appropriate percolation model to calculate the volume of change in the sensor from the change in resistance.

The sensor arrays are suitable for large scale production using integrated circuit technology. The

chemoresistors and quartz crystal microbalance sensors can be integrated onto the front end of an amplifier interface to and Analogue to Digital (AD) convertor (not shown) to feed the data stream to an analyser which can be implemented by hardware or by neural network software. A sensor array having a very large number of sensors can be manufactured using integrated circuit design techniques, allowing the production of analyte sensors that are sensitive, small and portable.

The embodiment hereinbefore described relates to a analyte sensors and to a sensor array for use in conjunction with measuring devices for detecting electrical resistance across each chemoresistor and a change in resonance of the quartz crystal imbalance the measuring device being implemented by a computer, a database of sensor array response profiles and a comparison algorithm.

In an alternative embodiment, the electrical measuring device is an integrated circuit comprising neural network-based hardware and a digital-analogue converter (DAC) multiplexed to each sensor, or a plurality of DACs each connected to different sensors. In yet a further embodiment, the chemoresistors, the quartz microbalance, the neural network-based hardware and the DACs are all located on a single integrated circuit.

It will be appreciated that various modifications may be made to the embodiment hereinbefore described, without departing from the scope of the invention. In particular, it will be appreciated that the volume-changing sensors 12 may be loaded with a silver/gold colloid, a conducting polymer or a redox metal complex instead of carbon black. The volume-changing sensors response may be based on an optical, thickness-sensitive technique such as surface plasmon resonance spectroscopy or a capacitance/complex impedance sensor rather than electrical resistance which would in many cases obviate

the need to load the volume sensitive membrane with conducting material. The mass changing sensor 14 may be a surface acoustic device instead of a quartz crystal microbalance. This would allow a chemoresistor to be incorporated into the surface acoustic device so that the interdigitated electrodes used to create the oscillating signal may also be used to act as the interdigitated electrodes for conductivity measurements performed by chemoresistors. Alternatively, a quartz crystal microbalance may be adapted to contain an extended electrode encircling the quartz crystal. The leads 42 may be made of any other suitable conducting metal or materials. Alternative flow systems to that shown in Fig. 1 may have the sensors 12,14 disposed in open air, or sensors moving between one area without a particular odourant or mixture of vapours to another area which has an odourant or mixture of vapours, or the sensors could be used for measuring a change in concentration of odourants or mixtures of vapours already present.

The principal advantage of the present invention is that, because the measurements determine the molecular density of an analyte which is constant for any given analyte rather than determining a resistance which relates to the analyte-impregnated polymer, it is possible to determine whether the host fluid being examined contains a mixture of different analytes. Furthermore, because the molecular density of an analyte is a constant for any given analyte, it is simpler to train an analyte recognition system based around volume-changing sensors and mass-changing sensors. Moreover, a wide variety of analytes and fluids may be analysed by the sensor array as long as the subject analyte is capable of generating a differential response across a plurality of sensors of the array. Non-exhaustive commercial applications of the sensor arrays include environmental, toxicology and remediation, biomedicine,

materials, quality control, food and agricultural products monitoring veterinary science, chemical process control, detection of organometallic or halogenated compounds.

The following examples are offered by way of illustration and are not to be construed as limiting thereof.

EXAMPLES

Chemoresistor Fabrication

Chemoresistor sensors were fabricated according to the method disclosed in PCT application no. WO 96/3075D. Chemoresistors were fabricated as multi-fingered interdigitated electrodes with gap sizes of either 10 or 40μm and an effective length of 10 cm. These electrodes were functionalised by spin coating at 2000rpm using a solution of 10g of chloroform containing 200mg poly(ethylene oxide) (Aldrich) and 50mg carbon black (Cabot Co, Billerica, USA).

Quartz Crystal Microbalance (QCM) Fabrication

The QCM sensors were 10 MHZ cut quartz crystals (ICM Co, Oklahoma, USA) spin coated with a solution of 200mg dissolved poly (ethylene oxide) in 10g of chloroform. From Figs 3a and 3b it will be seen that electrodes 49 are positioned to overlap to define the mass sensitive region, being the area in which the quartz crystal 48 oscillates.

Sensor Array Testing

Vapours were mixed and passed over the sensors using a regulated flow system enabling the measurement of simultaneous QCM and chemoresistor responses (Figure 1). Fig. 4 illustrates changes in frequency and resistance of the respective QCM and IE sensors on exposure to n-hexane, water and chloroform. In the depicted experiment, the vapour pressures of the different compounds were regulated to give similar values of resistance change and thus emphasise the difference in magnitude of the frequency change. As illustrated,

chloroform gave the largest frequency (mass) change for the given resistance change, and hexane the smallest. The rate of change of the response of the sensor types is different for each vapour, but follow each other closely. For both water and chloroform, the shapes of appropriately normalised traces from IE and QC sensors are indistinguishable.

Under suitably optimised conditions, after exposure to a vapour, the volume-change in the chemoresistor is proportional to the number and size of sorbed vapour molecules, i.e. the total molecular volume occupied by the sorbed species within the polymer. Thus, by determining the increase in the mass of the polymer film on sorption of a vapour, and using changes in the chemoresistance to quantify the corresponding volume-change, the sorbed species' molecular density is readily calculated

To better understand the relationship between changes in sorbed mass and polymer volume, Fig. 5 illustrates the ratio of QCM frequency change to IE resistance change for a variety of gasses which cover a wide range of densities (liquid density range from 0.66g cm^{-3} to 1.49g cm^{-3}). To facilitate comparison between sensors of differing film thicknesses, this ratio is normalised to the film's dry mass (frequency, f_o), and dry resistance (R_o), leading to the ordinate function $(\Delta f/f_o)/(\Delta R/R_o)$. The vapours used in this example include representatives from both hydrophobic and hydrophilic species, polar and non-polar species, and isotopically substituted species.

Fig. 6 shows a plot of percentage frequency change against percentage resistance change for different CH_2Cl_2 vapour pressures (9.2mm Hg to 138mm Hg). The plot is linear over the concentration range studies, although it should be noted that a non-zero intercept obtained from an unconstrained best fit line (not shown) may reflect the influence of the bath gas (N_2) on the polymer

composite's swollen state.